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Title :A review of the longevity of effect of Botulinum Toxin in wrinkle treatments.

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Abstract

Abstract

Botulinum toxin is widely used in facial rhytide treatments. The duration of its effect's influences treatment intervals, cost and convenience to the patient. These are key factors in successful aesthetic procedures. A review of the literature found that duration of effect was between 2 and 6 months, with most experiencing loss of maximal contraction for 3-4 months. Treatments may last between 3-4 months, and occasionally up to 6 months. No specific definition of effectiveness/ efficacy has been described and used to measure comparable end points. Additional research should help clarify the impact of brand, age, gender, ethnicity, repetition of treatment and zinc-phytase supplementation.

Clinical Relevance

The aim of this review article was to ascertain the duration of action of Botulinum toxin type A in the treatment of glabellar frown lines ¹ in order to provide evidence based advice to patients by ascertaining the average length of time a patient perceives their aesthetic botulinum toxin treatment lasts, and compare that to the published values.

Background

The neurotoxin produced by the bacterium *Clostridium botulinum*, Botulinum toxin, was first identified in 1897.² It can produce muscle weakness or paralysis that has been exploited for treatments of muscle hyperactivity. It was first used by Dr. Alan Scott to treat strabismus³ and subsequently prescribed for the treatment of muscle spasms in many other areas of the body. Scott concomitantly predicted other potential future applications, including a role in providing cosmetic enhancement.

The purified crystallised toxin serotype A (specifically BotoxTM) was initially given FDA approval in 1989 for the treatment of involuntary muscle disorders such as strabismus.² In 1993 Blitzer et al. described the use of the toxin for the management of 'hyper-functional lines of the face'; a cosmetic use was thus born⁴. The latter worked by impeding the underlying muscle contraction causing relaxation and thus flattening of the overlying skin. Since then, its use in the treatment of rhytides (wrinkles) has spread considerably, with the global market forecast to hit \$2.9 billion by 2018 according to Global Industry Analysts Inc.⁶ Indeed there has been a very large rise, with a spiralling increase in the number of patients seeking aesthetics treatments, with the market growing 6% in 1 year alone.⁷ A study by the UK Department of Health in 2013 estimated that 75% of the cosmetic market value in the UK is accounted for by Botulinum Toxin A and other non-surgical procedures.⁸

Owing to the dental origin of such aesthetic changes, the dental surgeon is ideally placed to diagnose and treat facial concerns; hence there is a great overlap in these fields. As the dentist is trained in head and neck anatomy, and performs injections regularly as part of their routine work it may follow that this procedure should become part of their practice. There are several well accepted techniques using Botulinum toxin around the oral cavity, such as treatment of the 'gummy-smile' or 'smokers lines' in the upper lip. These are currently off-label uses for the toxin, and as such studies and clinical data are comparatively scarce. It is for this reason that this review focuses on the better studied, on-label, treatment of the glabellar region in order to achieve some homogeneity of studies compared.

In the UK, only three preparations of Botulinum Neurotoxin type A are licensed for the treatment of glabellar lines; OnabotulinumtoxinA (Botox/Vistabel, Allergan), IncobotulinumtoxinA (Bocouture/Xeomin, Merz) and AbobotulinumtoxinA (Azzalure/Dysport, Ipsen.).⁹

The Pharmacological Effects of Botulinum Toxin

Neuromuscular transmission is usually achieved when the neurotransmitter acetylcholine is transported to presynaptic terminals (the nerve endings) in membrane vesicles which fuse with the cytoplasmic membrane leading to release of the neurotransmitter into the neuromuscular junction. (This is the process which administration of Botulinum toxin blocks.) From here it diffuses across the synaptic gap to bind with the nicotinic cholinergic receptors on the

postsynaptic membrane of the muscle surface.¹⁰ The effect of preventing neurotransmission at motor nerve endings is to temporarily denervate and hence relax the muscles local to the injection site.⁴

It is not yet known how the toxin is metabolised or otherwise eliminated from nerve endings.¹¹ Indeed, there remain some considerable gaps in our knowledge of the mechanism for absorption, distribution, metabolism and elimination of the toxin.¹² However, it has been postulated that the toxin binds irreversibly to the synaptic nerve endings, and is then metabolised over the proceeding months. It is likely that the protein degrades and is removed by the body and the pharmacological effects then ceases.

There is no evidence of muscular atrophy following repeated Botulinum toxin injections over long periods of time, but there have been incidences of resistance by antibody development. Certainly, with Botulinum toxin treatments being so common, it follows that with greater numbers of treatments the number of incidents of immunity should rise. The latter has been reported to be rare; Kawashima and Harii found no incidence of antibody formation when testing the 363 subjects of their 2009 study.¹³ There is also no evidence of hypersensitivity developing. However, potential behavioural modification whereby the patient learns to avoid 'undesirable' facial movements may occur.⁴

Applications in Medical Dystonias and Aesthetics
Strabismus and other ocular motility applications
Focal cervical
Oromandibular and laryngeal dystonias
Blepharospasm (focal dystonia of the orbicularis oculi)
Spasticity relating to Multiple Sclerosis and other neurological conditions
Tennis elbow and other muscular pains
Bell's Palsy
Hyperhidrosis
Chronic migraines (FDA approval 2010)
Over active bladders (approved in 2011).
Glabellar rhytides

Figure 1: Different applications for Botulinum toxin A ^(1,14).

The therapeutic scope of the Toxin is quite varied (Figure 1) Botulinum toxin has been used cosmetically since its cosmetic effects were documented in 1989. In facial aesthetic treatments, the toxin works by causing weakening of the underlying muscle which exhibits habitual contraction, causing relaxation and thus flattening of the overlying skin. ⁴ The use of Botulinum toxin for treatment of facial rhytides is 'off-label' (an unlicensed, but well accepted use) aside from glabellar lines and thus should be explained to the patient at point of consent.⁴

How the effects may be determined as ongoing

For ongoing effects to be assessed and measured, it is important to clarify what constitutes 'effective'. This is a very difficult question as the degree of effect varies, and the methods of assessing and measuring it are diverse.

Electromyographic (EMG) Guidance has been documented as an aid to locate where to inject the toxin. Although 'in neurologic indications EMG represents the gold standard for detection of muscular activity, the spatial resolution of this method probably limits its usefulness in aesthetic applications.'¹⁵ Studies have used a scoring system such as the Facial Wrinkle Score in order to assess the effect of toxin therapy. These are very subjective criteria and may vary between different assessors, and a disadvantage is they are subject to body dysmorphia if self-assessment is used.

Bhatnagar and co-workers¹⁶ have described the 'digital image speckle correlation' whereby skin detail such as the pores of the skin are used to map changes in skin surface overlying the muscles and thus 'track the degree of contraction' and associated skin displacement.

None of the methods investigated for measuring or quantifying longevity gives a good standard, as there is no consensus on what is 'effective', nor a quantifiable, reproducible method by which to measure it. Only once 'effective' is defined, can duration be assessed.

The patients' perceived outcomes are hugely important as this is what will contribute to patient satisfaction and as a result either repeat business or conversely, complaints. It is however, subjective, and there may be many factors which influence the patients' self reporting.^{17, 18, 19} As these elective treatments have a cosmetic, rather than a therapeutic value, the psychological health of a patient will hugely influence their perceived success as patients with Body Dysmorphic Disorder do not typically benefit from cosmetic procedures²⁰.

Among the studies included there were 7 very different methods for assessing effective duration;

- 1 Patient perceived duration
- 2 Investigator-assessed wrinkle severity (by various subjective scales; FWS, GLSS)P
- 3 Patient self assessed wrinkle severity (as above)
- 4 Skin movement at maximal contraction
- 5 Improvement at repose
- 6 Length/depth of rhytide at maximal contraction compared to baseline
- 7 Treatment intervals ²¹

Ascher et al.²¹ used the time between first and second injection as their measure of duration. Repeat treatment intervals may be used to gauge how long a patient feels the treatment lasted satisfactorily. However, there are other factors; availability of clinics, cost of treatments, social factors around access to treatment such as time, distance, perceived healing time. The choice of outcome measures differs greatly; quantitative DISC, and the more subjective assessment by both the plastic surgeon and the patient showed a clear correlation. However, the reappearance of muscle contraction (DISC) preceded the wrinkle appearance for patients by 4-8 weeks, demonstrating that potentially the wrong measure was employed.¹⁷

Eight of the studies used patient assessment as at least one measure. This is relevant in a clinical setting, as the patients perceived benefit would be a huge influencer on their satisfaction and potential repeat business. It is however fraught with potential bias where the patient is aware of the desired outcome and also potentially the influence of cost and access where treatment intervals are concerned.

Dailey et al.²² used patient photographs, which limited their population to lighter skin tones in order to be able to clearly image the rhytides. This variation in method obviously produces results that cannot be compared, that in the main-part measure something that although measurable, or subjectively quantifiable, is in truth not the effect that should be being considered for aesthetic purposes. The durations of effects have been simplified by averaging out where possible, but it is important to note that in many cases the duration was deemed to go

beyond the length of the study and as such these studies are a guide that effects are on-going, but not a measure of the actual longevity.

It does not appear that there is an obvious pattern in assessment method and duration. Certainly, the patient perceived endpoint, which is weaker in terms of evidence has a shorter duration, so it may suggest that the longer durations are a better indicator.

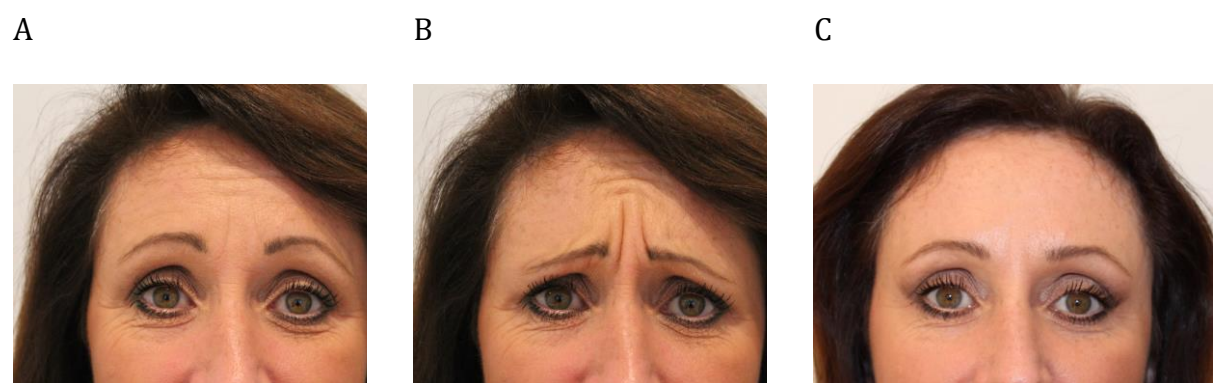


Figure 2: Photographs to show glabellar frown lines a) at rest and b) at full contraction, then c) 2 weeks following treatment with Botulinum toxin.

Factors that can affect the longevity of Botulinum toxin treatment?

There are many variables in treatments with Botulinum toxin, both in the manner in which it is administered, and also the subject in which it is injected. If we know their effect, we may optimise results and give better advice.

Dose of toxin used, and its effect on longevity.

Reduced dosages may result in unacceptably short durations.²³ Whilst a higher dose may be found to last longer, this must be weighed against higher doses potentially spreading to adjacent muscles with potentially adverse effects, and also the increased cost to the patient.

A study by Hankins et al.²⁴ found there to be no significant difference in the longevity of effects from injection doses of 4-10 U per site. Moreover, lower volumes used at a higher concentration were reported to be less uncomfortable, should have less spread, and thus be less likely to affect areas beyond the intended site.

Studies which test doses lower than recommended in the product information may be useful, as this may be common in practice, as they would be cheaper, and could also explain some poor treatment durations, and justify why clinicians should use the recommended doses.

Dose may not actually be comparable between products, and needs further investigation. Although there are conversions suggested between Speywood units, these vary in the literature, and may vary in different applications.

Where the durations are shown in order of dose, there is no clear pattern to suggest a good correlation. The doses are, however, mainly similar, and there are many other variables in the study designs. In addition, the doses are often altered to reflect for example the muscle mass, so higher doses may be being used in larger muscles.

Previous studies by Caruthers and co-workers²⁵ and Lowe and co-workers²⁶ reported that higher doses are more efficacious for longer in the applications they studied. This result was corroborated by Harii and Kawashima (2008)²⁷ who found the mean duration rose from 7.9 weeks for 10U to 9.4 weeks for 20U. The study by Grimes et al. (2009)²⁸ however suggests that 30U is no more effective than 20U in this small sample, so there may be an optimal dose. In fact Kane et al.²⁹ found that as the dose increased, the percentage of responders decreased. However, it was suggested this was because those given larger doses were those with a greater muscle mass, and therefore were likely to be worse responders, so that this result was not directly related to the dose given. This would potentially impact on the gender results, as men tend to have greater muscle mass than women.

Licensed doses limit the study of the effect of dose on longevity, and so it is sensible that future research should include this in the study.

Location

Area of treatment may impact treatment efficacy and duration. In a study by Blitzer et al. better results were found in the forehead than glabellar region (Figure 2), however, this study concentrates on the glabellar alone.



Figure 3: Photograph of Botulinum toxin being administered to the glabellar region.

Number of injection sites

Figure 3 (below) shows that most of the studies employed 5 injections sites (1 mid-line in the procerus, and 2 each side in the glabellar (see figure 2 above), in slightly different positions in some American studies) and there was no evidence to suggest the number of sites influences duration.

Study	Intervention		Outcome
	Type of toxin (AbobotulinumtoxinA = A, IncobotulinumtoxinA = I, OnabotulinumtoxinA = O)	Total Glabellar Dose/(no. injection)	Duration (days)
Kassir, 2013 30	A, O	8U Ona, 20 Speywood Units Abo	27% 150 A, 2% 150 O
Harii and Kawashima, 2008 27	O	10-20U/(5)	65.8 (20U) 55.3 (10U)
Jandhyala, 2015 9	A, I, O	NR	A- 111, I-125, O- 108
Banegas et al., 2013 31	O, I	Mean 15.2U- O, 15.3U-I	O- 180, I-144
Kane et al.,	A	50-80	92.8

2009 29		Speywood Units	
Grimes and Shabazz, 2009 32	0	20-30U/(5)	80-90% 120+
Lowe et al., 1996 26	0	20U/(2)	124.6
Dailey et al., 2011 22	0	20U/(5)	42% 168+
Imhof, 2011 33	I	20U/(5)	80% 84+
Prager et al., 2013 34	I	25U/(5)	75% 150+
Proebstle et al., 2014 35	I	30U/(6)	168+ (1/2 unit improvement)
Moy et al., 2009 36	A	50U/(5)	88

Figure 4 shows mean durations in each study relative to dose used. Toxin type also shown.

Supplements

It has been found that zinc is required in the action of the light (50kDa) chain. During translocation into the cytoplasm the light chain is denatured and the chelation site loses zinc, then having to regain another zinc from the cytosols ambient pool.³⁷ As a result recent studies suggesting zinc may have an effect on the action of the toxin binding and hence potentially implications on longevity. There was no mention of zinc as a variable in any of the papers reviewed, however, recent widespread press coverage²⁶ has created interest from patients who wish to know if the addition of zinc is a viable method of increasing treatment longevity. According to the study by Koshy et al. (2012)³⁸ 92% of participants who received supplementary dietary zinc in combination with Phytase supplements (phytase is believed to improve zinc absorption) had an increase in longevity. The level of evidence however, is still poor as the patient sample receiving the zinc- phytase supplement marketed as 'Zytase' was relatively small³⁸, and the author had a financial interest in the supplement. Therefore evidence is sparse and future research is needed in this area,³⁹ especially as there is no scientific explanation why this effect should be found, nor is it known if those in the study were deficient in either zinc or phytase as suggested, such that the pool of zinc might have been sufficient without supplementation.

Brand

As can be seen in Table 1 almost all the research is based on trials of one brand, the end result of each is arguably only specific to that brand. This could be another variable on the longevity of effect in itself. Most of the research published has been carried out with editorial assistance or funding by one of the major pharmaceutical companies who produce the toxins. As such visibly unbiased discussion is lacking. The toxins are expensive, and a large scale trial, with all three of these licensed preparations would require significant funding.

Despite heterogeneity between studies, those with direct comparisons suggest that AbobotulinumtoxinA (Allergan, Dysport – please refer to Figure 4) is superior to OnabotulinumtoxinA (Botox, Allergan), and IncobotulinumtoxinA (Bocouture, Merz) may be even better, as the remainder of the studies using this toxin find the results to be ongoing at the end of the study duration, so no end point can be clearly extrapolated. This is illustrated in Figure 3.



Figure 5: Photograph of two of the brands commonly used in the UK.

Skin type

An earlier study comparing skin structure in females of 4 different ethnic groups found that the sub-epidermal non-echogenic band, which is less pronounced in African Americans, is a sensitive marker of skin ageing. OCT imagery was used to show that the thickness of the dermal–epidermal junction (DEJ) decreased with age, but remained higher in African Americans than in Caucasians, confirming that skin ageing is delayed in African Americans compared with all other ethnic populations.⁴⁰

The best comparison among the studies would be between the studies by Dailey et al. (2009)²² and Grimes et al. (2009)³². Sample sizes are similar^{18, 41} and both use 100% female patients, injected on 5 occasions with OnabotulinumtoxinA.

Unfortunately the studies are heterogeneous, as the age ranges differed but the mean age was 43.7²². If we only compare the results where the same dose was used (20U), by 4 months, patients in the group with Fitzpatrick types V/VI were still 60% satisfied, but there were only approximately 10% with response at maximum frown, as rated by both the patient and the assessor. There was however no blinding in the latter of these two trials. Therefore although the results appear to suggest a better longevity of effect in the lighter skin tones this is likely to be because these studies had less robust control on the assessment, and methods across the studies were heterogeneous so they cannot be directly compared. In fact

Kane et al. found duration of effect to be slightly greater in African American subjects²⁹.

Treatment repetition

Dailey et al.²² state that it is conceivable that further wrinkle reduction may be achieved with a treatment regimen that extends beyond 20 months²², but there is paucity of data for treatments longer than 1 year. The study found that satisfaction improved with each treatment cycle, arguably those who were unsatisfied may be more likely to drop-out.

Conclusion

One of the most important points from the results is that there is no average duration of effect, as so many of the end points are beyond the end of the time allocated to the study. No less than 5 of the studies included in the literature review found the effects to be ongoing past the last patient follow-up. In one study longevity was found to be between 10-21 weeks, while another study estimated 3- 6 months longevity, which is arguably not precise enough to be very helpful to patients as a guide. The figures are so diverse that there is no simple advice that can be gleaned from it to inform patients. The effects may last between 2 and over 6 months. Furthermore the manner in which these results are measured may render these results inaccurate, as these studies reflect the perceived endpoint, and treatment intervals respectively, which are two different measures. Moreover, the majority of studies examined the duration of the effect of the toxin on Maximal Contraction not on wrinkle appearance at rest, which is in fact arguably the pertinent issue, as this is what most patients seeking

glabellar treatment with toxin would want to achieve. One factor that was less well assessed in studies was that of practitioner competence, as these studies were often single practitioners, and none were students or trainees. This is likely to be a hugely influential factor in the successful outcome and longevity of the treatment as it may influence dose, position of injection and also communication with the patient.

Summary.

In summary the current advice on longevity is flawed, as it is often based on the duration of loss of maximal contraction, and therefore not really describing the effect most patients probably seek. In review, having assessed what we know of how the different variables affect treatment duration it is possible to draw some conclusions and possible patient advice. The desirable duration of effect may differ according to its application. Advising not only on the duration, but understanding the factors that may influence this could be used to achieve the most desirable duration for any given case.

Variable longevities of effect would be useful, as longer treatment durations reduce patient cost, and repeat visits, but shorter durations of effect may also be used to immobilise areas post-surgery. In the case of aesthetic treatments this could be a potential selling point for those patients who are unsure, and wish to 'try' a treatment before they commit.

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